STRUCTURE FILE UPDATES: 7 SEP 2011 HIGHEST RN 1329744-16-2 DICTIONARY FILE UPDATES: 7 SEP 2011 HIGHEST RN 1329744-16-2

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chain nodes : 7 8 9 16 17 18 19 20 21 22 23 24 25 26 27 28 30 ring nodes : 1 2 3 4 5 6 10 11 12 13 14 15 chain bonds : 3-30 6-7 7-8 7-9 9-10 12-16 16-17 17-18 18-19 18-22 19-20 19-21 22-2322-24 23-27 23-28 24-25 24-26 ring bonds : 1-2 1-6 2-3 3-4 4-5 5-6 10-11 10-15 11-12 12-13 13-14 14-15exact/norm bonds : $1-2 \quad 1-6 \quad 2-3 \quad 3-4 \quad 3-30 \quad 4-5 \quad 5-6 \quad 7-8 \quad 7-9 \quad 9-10 \quad 10-11 \quad 10-15 \quad 11-12 \quad 12-13$ 13-14 14-15 16-17 17-18 19-20 19-21 22-23 24-25 24-26 exact bonds : 6-7 12-16 18-19 18-22 22-24 23-27 23-28

G1:C, I

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:Atom 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:CLASS 17:CLASS 18:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS 30:CLASS

L1 STRUCTURE UPLOADED

=> d

L1 HAS NO ANSWERS

Structure attributes must be viewed using STN Express query preparation.

=>
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chain nodes : 7 8 9 16 17 18 19 20 21 22 23 24 25 26 27

ring nodes :

1 2 3 4 5 6 10 11 12 13 14 15

chain bonds :

 $6-7 \quad 7-8 \quad 7-9 \quad 9-10 \quad 12-16 \quad 16-17 \quad 17-18 \quad 18-19 \quad 18-22 \quad 19-20 \quad 19-21 \quad 22-23 \quad 22-24$

23-27 24-25 24-26

ring bonds :

 $1-2 \quad 1-6 \quad 2-3 \quad 3-4 \quad 4-5 \quad 5-6 \quad 10-11 \quad 10-15 \quad 11-12 \quad 12-13 \quad 13-14 \quad 14-15$

exact/norm bonds :

 $1-2 \quad 1-6 \quad 2-3 \quad 3-4 \quad 4-5 \quad 5-6 \quad 7-8 \quad 7-9 \quad 9-10 \quad 10-11 \quad 10-15 \quad 11-12 \quad 12-13 \quad 13-14$

14-15 16-17 17-18 19-20 19-21 22-23 24-25 24-26

exact bonds :

6-7 12-16 18-19 18-22 22-24 23-27

G1:C, I

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:Atom 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:CLASS 17:CLASS 18:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS

L2 STRUCTURE UPLOADED

=> d

L2 HAS NO ANSWERS

L2 STR

G1:C, I

Structure attributes must be viewed using STN Express query preparation.

=> s 11 full

FULL SEARCH INITIATED 15:25:43 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 50 TO ITERATE

100.0% PROCESSED 50 ITERATIONS 16 ANSWERS

SEARCH TIME: 00.00.01

L3 16 SEA SSS FUL L1

=> s 12 full

FULL SEARCH INITIATED 15:25:46 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 187 TO ITERATE

100.0% PROCESSED 187 ITERATIONS 42 ANSWERS

SEARCH TIME: 00.00.01

L4 42 SEA SSS FUL L2

=> fil caplus

COST IN U.S. DOLLARS SINCE FILE TOTAL ENTRY SESSION FULL ESTIMATED COST 393.72 393.95

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FILE COVERS 1907 - 8 Sep 2011 VOL 155 ISS 11

FILE LAST UPDATED: 7 Sep 2011 (20110907/ED)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2011

USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2011

CAplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2011.

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 13

L5 12 L3

=> d ibib hitstr abs 1-12

L5 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2010:168084 CAPLUS 152:279363
Inhibitory effects of (2s, 3s)-3-[3-4(trifluoromethyl)benzoylamino]benzyloxylaspartate
(TFB-TBOA) on the astrocytic sodium responses to glutamate
Bozzo, Luigi; Chatton, Jean-Yves
Department of Physiology, University of Lausanne, Switz.
Brain Research (2010), 1316, 27-34
CODEN: BRREAP; ISSN: 0006-8993
Elsevier B.V.
Journal
English DOCUMENT NUMBER: TITLE: AUTHOR (S) CORPORATE SOURCE: SOURCE PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT 480439-73-4, TFB-TB0A
RL: PAC (Pharmacological activity); BIOL (Biological study)
(inhibitory effects of (2S, 3S)-3-[3-[4(trifluozomethyl)benzoylamino]benzyloxylaspartate (TFB-TBOA) on
astrocytic sodium responses to glutamate)

RN 480439-73-4 CAPLUS
CN L-Aspartic acid,
3-[[3-[[4-(trifluozomethyl)benzoyl]amino]phenyl]methoxy], (3S)- (CA INDEX NAME) PHBLISHER:

Astrocytes are responsible for the majority of the clearance of extracellular glutamate released during neuronal activity. DL-Threo-β-benzyloxyaspartate (TBCM) is extensively used as inhibitor of glutamate transport activity, but suffers from relatively low affinity for the transporter. Here, we characterized the effects of (2S, 3S)-3-[3-[4-(trifluoromethyl)benzoylamino]benzyloxy]aspartate (TFB-TBOA), a recently developed inhibitor of the glutamate transporter on mouse cortical astrocytes in primary culture. The glial Na+-glutamate sport AB

port system is very efficient and its activation by glutamate causes rapid intracellular Na+ concentration (Na+ i) changes that enable real time of transporter activity. Na+i was monitored by fluorescence microscopy

L5 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2008:526914 CAPLUS

OCUMENT NUMBER:

2008:526914 (APLUS 149:97946 Fragmental modeling of human glutamate transporter EAAT1 and analysis of its binding modes by docking

pharmacophore mapping Pedretti, Alessandro; De Luca, Laura; Sciarrillo, Cristina; Vistoli, Giulio Istituto di Chimica Farmaceutica e Tossicologica "Pietro Pratesi", Facolta di Farmacia, Universita degli Studi di Milano, Milan, I-20133, Italy ChemMedChem (2008), 3(1), 79-90 CODEN: CHEMOK; ISSN: 1860-7179 Wiley-VCH Verlag GmbH AUTHOR(S):

CORPORATE SOURCE:

MENT TYPE: Journal WIGGE: English English English (180439-69-8 480439-73-4, TFB-TBOA RL: BSU (Biological study, unclassified); BIOL (Biological study) (fragmental modeling of human glutamate transporter EAATl and anal. of its binding modes by docking and pharmacophore mapping) 480439-69-8 CAPLUS L-Aspartic acid, 3-[[3-[(4-cyanobenzoyl)amino]phenyl]methoxy]-, (3S)-

CN (CA

Absolute stereochemistry.

480439-73-4 CAPLUS RN 40493-73-4 CREDS CN L-Aspartic acid, 3-[[3-[[4-(trifiluoromethyl)benzoyl]amino]phenyl]methoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.

L5 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Cont single astrocytes using the fluorescent Na+-sensitive probe (Continued)

single astrocytes using the fluorescent war-scale.

sodium-binding
benzofuran isophtalate. When applied alone, TFB-TBOA, at a concn. of 1

µM, caused small alterations of Na+i. TFB-TBOA inhibited the Na+i
response evoked by 200 µM glutamate in a concn. dependent manner with
IC50 value of 43 ± 9 nM, as measured on the amplitude of the Na+i
response. The max. inhibition of glutamate-evoked Na+i increase by
TFB-TBOA was > 80%, but was only partly reversible. The residual

response

persisted in the presence of the AMPA/kainate receptor antagonist CNQN.

TFB-TBOA also efficiently inhibited Na+1 elevations caused by the application of D-aspartate, a transporter substrate that does not activate
non-NMDA ionotropic receptors. TFB-TBOA was found not to influence the membrane properties of cultured cortical neurons recorded in whole-cell patch clamp. Thus, TFB-TBOA, with its high potency and its apparent law of neuronal effects, appears to be one of the most useful pharmacol.

tools

available so far for studying glial glutamate transporters.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS

(1 CITINGS)
THERE ARE 16 CITED REFERENCES AVAILABLE FOR

RECORD. ALL CITATIONS AVAILABLE IN THE RE

ANSWER 2 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

The objective of the study was to generate a reliable model of the homotrimeric structure for the human glutamate transporter EAAT1, based

exptl. folding of transporter homolog from Pyrococcus horikoshii. The monomer structure was derived using a fragmental approach and the homotrimer was assembled using protein-protein docking. The interaction capacities of the EARTI model were explored by docking a set of 32 known ligands including both substrates and blockers. Docking results unveiled that the substrates' bloactivity is strongly influenced by a precise fitting between the ligand and the EARTI binding site, whereas the blockers' activity depends on a set of apolar contacts that ligands can realize in an adjacent hydrophobic subpocket. The docking results were further verified by generating two pharmacophore models (the first for substrates and the latter for blockers) which revealed the features necessary for high EARTI activity. The consistency of docking results

and the agreement with pharmacophore models afford an encouraging validation for the EAAT1 model and emphasize the soundness of the fragmental approach

to model any transmembrane protein.
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS

RECORD

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2007:22602 CAPLUS 2007:22602 CAPLUS 146:244722 DOCUMENT NUMBER: Characterization of the tritium-labeled analog of L-threo-\$\tilde{\text{D}}\-\text{-benzyloxyaspartate} binding to glutamate transporters
Shimamoto, Keiko; Otsubo, Yasuto; Shigeri, Yasushi; Yasuda-Kamatani, Yoshimi; Satoh, Masamichi; Kaneko, Shuji, Nakagawa, Takayuki
Suntory Institute for Bioorganic Research,
Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka, Japan
Molecular Pharmacology (2007), 71(1), 294-302
CODEN: MORMA3; ISSN: 0026-895X
American Society for Pharmacology and Experimental
Therapeutics
Journal
English Characterization of the tritium-labeled analog of TITLE: AUTHOR(S): CORPORATE SOURCE: SOURCE. PUBLISHER: DOCUMENT TYPE: Journal
LANGUAGE, English
T 86437-05-3P
 RL: ARG (Analytical reagent use); PKT (Pharmacokinetics); SPN (Synthetic
preparation); ANST (Analytical study); BIOL (Biological study); PREP
(Preparation); USES (Uses)
 (characterization of tritium-labeled analog of
 I-threo-B-benzyloxyacpartate binding to glutamate transporters)
RN 86437-05-3 CAPLUS
CN L-Aspartic acid, 3-[[3-[[4-(ethyl-1,2-t2)benzoyl]amino]phenyl]methoxy]-,
 (3S)- (CA INDEX NAME) DOCUMENT TYPE:

Absolute stereochemistry.

L-Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. Termination of glutamate receptor activation and maintenance of low extracellular glutamate concns. are primarily achieved by glutamate transporters (excitatory amino acid transporters 1-5, EAATS 1-5) located on both the nerve endings and the surrounding glial cells. To identify the physiol. roles of each subtype, subtype-selective EAAT ligands are required. In this study, we developed a binding assay system to characterize EAAT ligands for all EAAT subtypes. We recently synthesized novel analogs of threo-P-benzyloxyaspartate (TBOA) and reported that they blocked glutamate uptake by EAATS 1-5 much more potently than TBOA. The strong inhibitory activity of the TBOA analogs

L5 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2006:656062 CAPLUS
145:124841
Preparation of β-benzyloxyaspartic acid derivatives as affinity-column ligands and glutamic acid transporter inhibitors

INVENTOR(S): Shimamoto, Keiko
Suntory Limited, Japan
POT Int. Appl., 23 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATICN: DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

													DATE						
W	2006	0707	37		Al		20060706		WO 2005-JP23773					20051226					
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		CN,	co,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,		
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	KE,	KG,	KM,	KN,	KP,	KR,	KZ,		
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JP 2006182696 JP 4008446 EP 1849766 R: AT, BE, BG,									EP 2	005-	8202	30	20051226						
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										WO 2	005-	JP23	113		N 2	OOST	226		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(8):

MARRAT 146:124841

R1: ARG (Analytical reagent use); BUU (Biological use, unclassified); PAC

(Pharmacological activity); SFN (Synthetic preparation); THU (Therapeutic

use); ANST (Analytical study); BIOL (Biological study); PREP

(Preparation); USES (Uses)

(preparation); USES (Uses)

(preparation); USES (Uses)

RN 896712-90-6 CAPLUS

CL -Aspartic acid,

3-[[3-[(28-amino-1,8,15-trioxo-17,20,23,26-tetraoxa-7,14-diazaoctacos-1-y1)amino]-5-[[4-(trifluoromethyl)benzoy:]amino|benyl]methoxy]-, (3S)-,

bis(trifluoroacetate) (9CI) (CA INDEX NAME) ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

EXR: Michael Barker

ANSWER 3 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued) suggested that they would be suitable to use as radioisotope-labeled ligands, and we therefore synthesized a tritiated deriv. of (2S, 3S) -3-(3-[4-ethylbenzoylamino]benzyloxy|aspartate ([3H]ETB-TBOA).
[3H]ETB-TBOA showed significant high-affinity specific binding to EAAT-transfected COS-1 cell membranes with each EAAT subtype. The Hill coeff. for the Na+-dependence of [3H]ETB-TBOA binding revealed a single class of noncooperative binding sites for Na+, suggesting that Na+ ling class of noncooperative binding sites for many augusting that his in the ligand binding step is different from Na+ binding in the substrate uptake process. The binding was displaced by known substrates and blockers. The rank order of inhibition by these compds, was consistent with glutamate uptake assay results reported previously. Thus, the [3H]ETB-TBOA binding assay will be useful to screen novel EAAT ligands for all EAAT subtypes.
OS.CITING REF COUNT: THERE ARE 6 CAPLUS RECORDS THAT CITE THIS (6 CITINGS) THERE ARE 39 CITED REFERENCES AVAILABLE FOR REFERENCE COUNT: RECORD. ALL CITATIONS AVAILABLE IN THE RE

ANSWER 4 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN CRN 896712-89-3 (Continued) CMF C41 H59 F3 N6 O13

Absolute stereochemistry. Rotation (-).

HO2C (CH₂)5 (CH₂)5

PAGE 1-B

PAGE 1-A

CRN 76-05-1 CMF C2 H F3 O2

896712-92-8 CAPLUS L-Aspartic acid, 3-[[3,5-bis[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, (38)-,

ANSWER 4 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN mono(trifluoroacetate) (9CI) (CA INDEX NAME) (Continued) CM 1 CRN 896712-91-7 CMF C27 H21 F6 N3 O7 Absolute stereochemistry. CMCO2H 896712-94-0 CAPLUS
L-Aspartic acid, 3-[[3-[(1-oxopropyl)amino]-5-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, (3S)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME) CM 1 CRN 896712-93-9 CMF C22 H22 F3 N3 O7 Absolute stereochemistry.

ANSWER 4 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

CO2F

GI

ANSWER 4 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

linear or branched aliphatic group optionally having nitrogen or oxygen in the chain, (un)substituted aromatic group] and salts thereof were prepared For example, treatment of compound II [R = tert-butyl; R' = tert-butoxycarbonyl] with trifluoroacetic acid afforded compound II [R, R' = H] with trifluoroacetic acid afforded compound II [R, R' = H]
trifluoroacetic
acid salt in 84% yield. In glutamic acid uptake inhibition assays, IC50
values of compound 11 [R, R' = H] **CF3CO2H for EAAT2 and EAAT3 were
1.3 and 0.46 nM, resp. A method of purifying or detecting an L-glutamic
acid transporter using compds. 1 is provided.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS
RECORD (4 CITINGS)
THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE REFERENCE COUNT:

L5 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2006:129293 CAPLUS
DOCUMENT NUMBER: 144:324958

I 144:324958

AUTHOR(S): Shimamoto, Feiko
CORPORATE SOURCE: Suntory Institute for Bioorganic Research, 1-1-1
Wakayamadai, Shimamoto-e-cho, Mishima-gun, Osaka, 618-8503, Japan
SOURCE: Shinkel Kenkyu no Shinpo (2005), 49(6), 850-854
CODEN: SNNSAF; TSSN: 0001-8724

PUBLISHER: Jayaku Shoin Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

IT 480439-73-4, TFB-TBOA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(elucidation of glutamate transporter functions using selective inhibitors)
RN 480439-73-4 CAPLUS
CN L-Aspartic acid,
3-[[3-[[4-(trifluoromethyl]benzoyl]amino]phenyl]methoxy], (38)- (CA INDEX NAME)

Absolute stereochemistry.

A review. L-Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system(CNS). To terminate glutamate receptor activation and to protect neurons from excitotoxicity, extracellular glutamate conces. are strictly controlled by sodium dependent glutamate transporters (excitatory amino acid transporters 1-5: EAATS1-5) located in nerve endings and surrounding glia cells. Selective and potent inhibitors have served as important exptl. tools to identify the physiol. roles of transporters in the regulation of synaptic transmission or in

pathogenesis of neurol. diseases. A pharmacol. useful probe, threo- β -benzyloxyaspartate (DL-TBOA) which functions as a non-transportable blocker for all subtypes of EAATs, has emerged from modification of a known inhibitor threo- β -hydroxyaspartate (THA). Non-transportable blockers are indispensable because, unlike substrates, they do not cause heteroexchange. By comparing the effects of substrates and non-transportable blockers, physiol. roles of EAATs have been revealed. EAATs not only remove transmitter from synaptic clefts but

actively modulate neurotransmission. Moreover, higher affinity ligands have been developed as novel pharmacol. tools. TBOA analogs possessing bulky substituent on their benzene ring significantly inhibited labeled

ANSWER 5 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued) glutamate uptake, the most potent of compd. being (25, 38)-3-(3-[4-(tri-fluoromethyl) benzoyl-amino] benzyloxy) aspartate (TFB-TBOA). TFB-TBOA is genuinely non-transportable at ED and showed no effects on glutamate receptors. TFB-TBOA would be a suitable lead compd. for designing functionalized ligands from the perspective of its markedly high affinity for EAAT proteins.

2006:24201 CAPLUS 144:142897 DOCUMENT NUMBER: 144:142897
Facilitative effect of a glutamate transporter inhibitor (2S,3S)-3-[3-[4-(trifluoromethyl)benzylamino]benzyloxylaspartate on the expression of methamphetamine-induced behavioral sensitization in rats Fujio, Mayumi; Nakagawa, Takayuki; Suzuki, Yuichi; Satoh, Masamichi; Kaneko, Shuji Department of Molecular Pharmacology, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, 606-8501, Japan TITLE: ATTHOR (S): CORPORATE SOURCE: of Pharmaceutical Sciences, Kyoto University, Kyoto 666-8501, Japan Journal of Pharmacological Sciences (Tokyo, Japan) (2005), 99(4), 415-418 CODEM: JFSTGJ, ISSN: 1347-8613 Japanese Pharmacological Society Journal English SOURCE: CODEN. JPSTGJ, ISSN: 1347-8613

PUBLISHER: Japanese Pharmacological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

T 480439-73-4

RL: PAC (Pharmacological activity), BIGL (Biological study)

(facilitative effect of a glutamate transporter inhibitor

{[(trifluoromethyl)benzoylamino]benzyloxylaspartate on expression of methamphetamine-induced behavioral sensitization in rats)

RN 480439-73-4 CAPLUS

CN L-Aspartic acid,

3-[[3-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]
, (3S)- (CA INDEX NAME) Absolute stereochemistry.

L5 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2006:24201 CAPLUS

We examined the effects of a potent glutamate transporter inhibitor, (28,38)-3-(3-[4-(trifluoromethyl)benzoylamino)benzyloxy]aspartate (TFB-TBOA), on the expression of methamphetamine-induced behavioral sensitization in rats. Rats were i.p. treated with 2 mg/kg methamphetamine for 5 days and then challenged with 1 mg/kg methamphetamine. Intracerebroventricular administration of TFB-TBOA (0.1 nmol) 10 min before the challenge significantly facilitated the easion AB expressio

of behavioral sensitization. It had no effect on the locomotor

Of Denovation activation elicited by the challenge with methamphetamine in repeated-saline-treated

L5 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)
(non-sensitized) rats. These results suggest that central glutamate
transporters may play an inhibitory role in the expression of behavioral
sensitization to methamphetamine.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS

REFERENCE COUNT:

FORMAT

(1 CITINGS)
THERE ARE 15 CITED REFERENCES AVAILABLE FOR RECORD. ALL CITATIONS AVAILABLE IN THE RE

L5 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2011 ACS ON STN ACCESSION NUMBER: 2005:1042190 CAPLUS DOCUMENT NUMBER: 143:306541 TITLE: Preparation of radials-1-1 LUS COPYRIGHT 2011 ACS on SIN 2005:1042190 CAPLUS 143:306541 Preparation of radiolabeled 3-[3-(benzoylamino)benzyloxy]aspartic acid derivatives as glutamate transporter inhibitors
Shimamoto, Keiko; Saji, Hideo; Kuge, Yuji; Ueda,
Masashi; Satoh, Masamichi; Nakagawa, Takayuki
Suntory Limited, Japan
PCT Int. Appl., 47 pp.
CODEN: PIXXD2
Patent
Inglish
1 INVENTOR(S): PATENT ASSIGNEE(S): SOURCE: DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

	PATENT NO.					KIN	D	DATE			APPL	ICAT		DATE				
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	WO 2005090268			A1	A1 20050929			WO 2	005-	JP56								
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			GE,	GH,	GM,	HR,	ΗU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,
			LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,	NI,
			NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SM,
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ZW																		
		RW:	BW,	GH,	GM,	KE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,
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			EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,	IS,	IT,	LT,	LU,	MC,	NL,	PL,	PT,
			RO,	SE,	SI,	SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GΩ,	GW,	ML,
			MR,	NE,	SN,	TD,	TG											
	EP	P 1732864 A1 20061220				1220	EP 2005-721527						2	20050318				
		R:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,
			IS,	IT,	LI,	LT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR		
	JP	TP 2007529412 T 20071025					1025		JP 2	006-		20050318						
US 20080248485			A1	1 20081009				US 2	006-	5930		20060915						
PRIORITY APPLN. INFO.:									JP 2	004-	7911	6		A 2	0040	318		
								WO 2	005-	JP56	00	1	W 2	0050	318			

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OFTHER SOURCE(S): CASREACT 143:306541; MARPAT 143:306541
IT 864936-98-1P 864936-99-2P 864937-04-2P
RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic use); BlOL (Biological study); PREF (Preparation); USES (Uses)
(preparation of radiolabeled [(benzoylamino)benzyloxy]aspartic acid

vs.
as glutamate transporter inhibitors)
864936-98-1 CAPLUS
L-Aspartic acid, 3-[[3-[[4-(iodo-125I)benzoyl]amino]phenyl]methoxy]-,
(3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry

ANSWER 7 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

864936-99-2 CAPLUS L-Appartic acid, 3-[[3-[(4-iodobenzoyl)amino]phenyl]methoxy]-, (3S)- (CA INDEX NAME)

864937-04-2 CAPLUS L-Aspartic acid, 3-[[3-[(4-ethylbenzoyl)amino]phenyl]methoxy]-, (3S)-(CA

INDEX NAME) Absolute stereochemistry.

480439-73-4 864937-05-3D, tritium-labeled

ANSWER 7 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

Absolute stereochemistry

The invention provides a radiolabeled ligand which is highly selective

potent for glutamate transporters and is usable in specifically detecting the glutamate transporter. Specifically, the invention provides 3-[3-(benzoylamino)benzyloxy]aspartic acid (BzA-TBOA) having a radioactive

nactive substituent at the p-position of the benzoyl group, as well as esters or salts. Thus, [1251]I-BZA-TBOA was prepared from N,O-protected A-TBOA by acylation with 4-bromobenzoyl chloride, tributylstannylation,

substitution
reaction with Na125I, and deprotection. Glutamate transporter inhibitory
activity data are tabulated for compds. of the invention.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

ANSWER 7 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued) RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (prepn. of radiolabeled [(benzoylamino)benzyloxy]aspartic acid derivs.

(prepn. of radiolabeled [(benzoylamino)benzyloxy]s
as glutamate transporter inhibitors)
RN 480439-73-4 CAPLUS
CN L-Aspartic acid,
3-[[3-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy], (3S)- (CA INDEX NAME)

Absolute stereochemistry

864937-05-3 CAPLUS L-Aspartic acid, 3-[[3-[[4-(ethyl-1,2-t2)benzoyl]amino]phenyl]methoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry

тт RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) actant or reagent) (preparation); FALF (Preparation); Adactant or reagent) (preparation of radiolabeled [(benzoylamino)benzyloxy]aspartic acid

as glutamate transporter inhibitors)
864937-03-1 CAPLUS
L-Aspartic acid, 3-[[3-[(4-ethenylbenzoyl)amino]phenyl]methoxy]-, (3S)(CA INDEX NAME)

L5 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2005:299120 CAPLUS

DOCUMENT NUMBER:

LUS COPYRIGHT 2011 ACS on STN 2005:299120 CAPLUS 142:442183 A novel L-glutamate transporter inhibitor reveals endogenous D-aspartate homeostasis in rat pheochromocytoma MPT1 cells Koyama, Hayator Sekine, Masae; Furuchi, Takemitsu, Katane, Masumi; Nimura, Noriyuki; Shimamoto, Keiko, Nakajima, Terumi; Homma, Hiroshi School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo, 108-8641, Japan Life Sciences (2005), 76(25), 2933-2944 CODEN: LIFSAK; ISSN: 0024-3205 Elsevier B.V. Journal AUTHOR(S):

CORPORATE SOURCE:

CODEN: LIFSAK; ISSN: 0024-3205

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal
LANGUAGE: English

T 480439-73-4

RL: BUU (Biological use, unclassified); PAC (Pharmacological activity);
BIOL (Biological study); USES (Uses)

(glutamate transporter inhibitor reveals endogenous D-aspartate homeostasis in rat pheochromocytoma MPTl cells)

RN 400439-73-4 CAPLUS

CN L-Aspartic acid,
3-[[3-[[4-(triflucomethyl)benzoyl]amino]phenyl]methoxy]
, (3S)- (CA INDEX NAME)

Absolute stereochemistry

We previously reported for the first time that D-aspartate (D-Asp) is biosynthesized by cultured mammalian cells such as pheochromocytoma AB

cells and its subclone MPT1 (FEBS Lett. 434 (1998) 231, Arch. Biochem Biophys. 404 (2002) 92). We speculated that D-Asp levels in the intr and extracellular spaces of the cultured cells are maintained in a

mic state of homeostasis. To test this here, we utilized a novel and potent L-Glu transporter inhibitor, (2S,3S)-3-(3-[4-(trifluoromethyl)benzyloylamino|benzyloxylaspartate (TFB-TBCA). This inhibitor proved to be a genuine nontransportable blocker of the transporter even during long periods of culture. Use of this inhibitor with MPTI cells confirmed that D-Asp levels are in a dynamic steady state where it is constantly released into the extracellular space by a yet undefined mechanism as well as being constantly and intensively taken up by the cells via the L-Glu transporter. We estimated the rate with which D-Asp is constitutively released from MPTI cells is approx. 3.8 pmol/h/1 x 105 cells.

L5 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)
OS.CITING REF COUNT: 7
THERE ARE 7 CAPLUS RECORDS THAT CITE THIS

REFERENCE COUNT: 42 (TITINGS)
THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS

FORMAT

L5 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)
excitability in CAI pyramidal cells. TFB-TBOA (100 nM) prolonged the
decay of N-methyl--aspartic acid receptor (NMDAR)-mediated excitatory
postsynaptic currents (EPSCS), whereas it prolonged that of
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
(AMPAR)-mediated EPSCs only when the desensitization of AMPARs was
reduced
by cyclothiazide (CT2). Furthermore, long-term application of TFB-TBCA
induced spontaneous epileptiform discharges with a continuous
depolarization shift of membrane potential. These epileptiform
activities
were mainly attributed to NMDAR activation. Even after pharmacol. block
of NMDARs, however, TFB-TBOA induced similar changes by activating AMPARs
in the presence of CT2. Thus, the continuous uptake of synaptically
released glutamate by glial transporters is indispensable for protecting
hippocampal neurons from glutamate receptor-mediated hyperexcitabilities.
OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS
RECORD (16 CITINGS)
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR
THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

L5 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2005;214287 CAPLUS

DCCUMENT NUMBER: 143:146338

Effects of a novel glutamate transporter blocker,
(2S, 3S) -3 -(3-[4(trifluoromethyl)benzoylamino]benzyloxylaspartate
(TFB-TBCA), on activities of hippocampal neurons

Tsukada, Shota; Lino, Masae; Takayasu, Yukihiro;
Shimamoto, Keiko; Ozawa, Selji

Department of Neurophysiology, Gunma University
Graduate School of Medicine, 3-39-22 Showa-machi,
Maebashi, Gunma, 371-8511, Japan

Neuropharmacology (2005), 48(4), 479-491

CODEN: NEPHBW; ISSN: 0028-3908

Elsevier B.V.

DOCUMENT TYPE: Journal
LANGUAGE.

RI: PAC (Pharmacological activity); BIOL (Biological study)
(effects of a novel glutamate transporter blocker,
(2S, 3S) -3 -3 - (4-(trifluoromethyl)benzoylamino]benzyloxylaspartate
(TFB-TBCA), on activities of hippocampal neurons)

NH 480439-73-4 CAPLUS

NH2

HN

NH2

NH2

NH2

NH2

NH2

AB Glutamate transporters rapidly take up synaptically released glutamate and maintain the glutamate concentration in the synaptic cleft at a low level. (2S, 3S)-3-{3-(4-(trifluoromethyl)benzoylamino|benzyloxy|aspartate (TFB-TBOA) is a novel glutamate transporter blocker that potently suppresses the activity of glial transporters. TFB-TBOA inhibited synaptically activated transporter currents (STCs) in astrocytes in the stratum radiatum in rat hippocampal slices in a dose-dependent manner with an IC50 of 13 nM, and reduced them to approx. 10% of the control at 100 nM. We investigated

effects of TFB-TBOA on glutamatergic synaptic transmission and cell

L5 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2004;469790 CAPLUS
DCCUMENT NUMBER: 141:184585
TITLE: Synthesis of carbamate-type caged derivatives of a novel glutamate transporter blocker
AUTHOR(S): Takaoka, Kiyo; Tatsu, Yoshiro; Yumoto, Noboru;
Nakajima, Terumi; Shimamoto, Keiko
CORPORATE SOURCE: Suntory Institute for Bioorganic Research, 1-1-1
Wakayamadai, Osaka, Shimamoto, 618-8503, Japan
Bioorganic &
Medicinal Chemistry (2004), 12(13),
3687-3694
CODEN: BMECEP; ISSN: 0968-0896
Elsewier Ltd.
COMBINE TYPE: Journal
LANGUAGE: CHEMICALE; CASERACT 141:184585
TIT 737830-21-6P
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP
(Preparation); FACT (Reactant or reagent)
(synthesis of carbamate-type caged derivs. of novel glutamate
transporter blocker:
RN 737830-21-6 CAPLUS
CN L-Aspartic acid,
3-[[3-[[4-(trifluoromethylethyl)] ester, (38)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

AB L-threo-β-Benzyloxyaspartate (1-TBOA) and

(2S,7S)-3-{3-4-(trifluoromethyl)benzoylamino|benzyloxy|aspartate
(L-TB-TBOA) are potent nontransportable blockers for glutamate
transporters. The authors synthesized a carbamate-type coumarin
derivative of
L-TBOA (3a) as a caged blocker and compared 3a with the corresponding
ester-type analogs 1. The carbamate 3a was less sensitive to photolysis
than the ester 1 but was more stable in the aqueous solution The
[6,7-bis(carboxymethoxy)-coumarin-4-yl]methylcarbonyl (ECMCMC) group
exhibited good results both in photoreactivity and stability. Therefore,
the authors examined photolysis of N-BCMCMC-TBOA and N-BCMCMC-TFB-TBOA,
which immediately released blockers to show glutamate uptake inhibition.
OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR
THIS

RECORD 16 CITINGS)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR
THERE ARE 26 CITED REFERENCES AVAILABLE FOR

L5 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued) L5 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2004:292674 CAPLUS

DOCUMENT NUMBER:

141:16890 Characterization of novel TITLE:

CORPORATE SOURCE:

DOCUMENT NUMBER: 141:16890

Characterization of novel
L-threo-β-benzyloxyaspartate derivatives, potent
blockers of the glutamate transporters

AUTHOR(S): Shimamoto, Keiko; Sakai, Ryulchi; Takaoka, Kiyo;
Yumoto, Noboru; Nakajima, Terumi; Amara, Susan G.;
Shigeri, Yasushi
SUNTOY Institute for Bioorganic Research, Osaka,
618-8503, Japan
Molecular Pharmacology (2004), 65(4), 1008-1015
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental
Therapeutics
Journal
LANSUAGE: English
IT 479690-57-8 480439-69-8 480439-73-4
RL: ADV (Radverse effect, including toxicity); PAC (Pharmacological
activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(characterization of novel
L-threo-β-benzyloxyaspartate derivs.,
potent blockers of glutamate transporters)

RN 479690-57-8 CAPLUS
CN L-Aepartic acid, 3-[[3-[4-(1,1dimethylethyl)benzoyl]amino]phenyl]methoxy]-, (33)- (CA INDEX NAME)

Absolute stereochemistry.

Absolute stereochemistry.

480439-69-8 CAPLUS L-Aspartic acid, 3-[[3-[(4-cyanobenzoy1)amino]pheny1]methoxy]-, (3S)-(CA

INDEX NAME)

Absolute stereochemistry.

ANSWER 11 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

RN 480439-73-4 CAPLUS CN L-Aspartic acid, 3-[[3-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.

Nontransportable blockers of the glutamate transporters are important tools for investigating mechanisms of synaptic transmission. DL-threo- β -Henzyloxyaspartate (DL-TBOA) is a potent blocker of all subtypes of the excitatory amino acid transporters (EAATS). We characterized novel L-TBOA analogs possessing a substituent on their AB

benzene rings. The analogs significantly inhibited labeled glutamate uptake, the most potent of which was (28,38)-3-(3-[4-(trifluoromethyl)benzylamino]benzyloxy)aspartate (TRB-TBOA). In an uptake assay using cells transiently expressing EAATs, the IC50 values of TFB-TBOA for EAATI, EAAT2, and EAAT3 were 22, 17, and 300 mM, resp. TFB-TBOA was significantly more potent at inhibiting EAAT1 and EAAT2 compared with L-TBOA (IC50 values for EAATI-3 were 33, 6.2, and 15 µM, resp.). Electrophysiol. analyses revealed that TBOA analogs block the transport-associated currents in all five EAAT subtypes and

block leak currents in EAAT5. The rank order of the analogs for

potencies at inhibiting substrate-induced currents was identical to that observed

the uptake assay. However, the kinetics of TFB-TBOA differed from the kinetics of L-TBOA, probably because of the strong binding affinity. Notably, TFB-TBOA did not affect other representative neurotransmitter transporters or receptors, including ionotropic and metabotropic

EXR: Michael Barker

L5 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)
receptors, indicating that it is highly selective for EAATs. Moreover,
intracerebroventricular administration of the TBOA analogs induced severconvulsive behaviors in mice, probably because of the accumulation of
glutamate. Taken together, these findings indicate that novel TBOA
analogs, esp. TFB-TBOA, should serve as useful tools for elucidating the
physiol. roles of the glutamate transporters.
OS.CITING REF COUNT: 44 THERE ARE 44 CAPLUS RECORDS THAT CITE THIS
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR
THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
L5 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER:
DOCUMENT NUMBER:
138:72990
TITLE:
Preparation of β-(aminobenzyloxy)aspartate
derivatives as glutamate transporter inhibitors
SOURCE:
SOURCE:
COEN. PIXXD2
PACENT TYPE:
Patent
Patent
 LANGUAGE:
FAMILY ACC, NUM. COUNT:
                                                   nglish
 PATENT INFORMATION:
          PATENT NO.
                                               KIND DATE
                                                                                   APPLICATION NO.
                                                                                                                             DATE
WO 2002-JP6286
                                                                                                                     W 20020624
                                                                                  US 2004-481237
                                                                                                                     A3 20040719
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT OTHER SOURCE(S):

(ASREACT 138:72990; MARPAT 138:72990

11 47969-57-8P, TBU-BEA-TBOA 47969-58-9P

480439-69-8P, CN-BEA-TBOA 480439-73-4P, CF3-BEA-TBOA

RL: FBAC (Fharmacological activity); SFN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
                 (preparation of (aminobenzyloxy)aspartate derivs, as glutamate
 transporter
          iporter
   inhibitors)
479690-57-8   CAPLUS
L-Aspartic acid, 3-[[3-[[4-(1,1-
dimethylethyl)benzoy1]amino]phenyl]methoxy]-, (3S)- (CA INDEX NAME)
 Absolute stereochemistry.
```

L5 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued) CN L-Aspartic acid, 3-[[3-[[4-(trifluoromethy1)benzoy1]amino]pheny1]methoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.

GI

AB L-Threo-β-benzyloxyaspartate derivs. I [R = H, (un) substituted acyl, an amino acid- or biotin-derived group] or their salts were prepared for binding to affinity column chromatog. carriers as ligands of glutamate transporter proteins. Thus, I (R = m-H2NCH2CH2CONH) (AA-TBOA) was prepared by a multistep synthesis starting with the reaction of (28,38)-(3-lbenzyloxymethyl)oxulranyl]methyl p-nitrobezoate with benzoyl isocyanate. The inhibitory effect of AA-TBOA was determined to be IC50 = 2.1

± 0.1 μM and 7.9 ± 0.76 μM, resp., for uptake of (14)glutamate by human EAAT2 or EAAT3 stably expressed on MDCK cells or transfertly expressed on COS-1 cells.

S.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

L5 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

NH2

Bu-t

RN 479690-58-9 CAPLUS
CC 1NDEX NAME)

Absolute stereochemistry.

NH2

CC2H

CC2H

RN 480439-69-8 CAPLUS
CC2H

CCA 1NDEX NAME)

RN 480439-69-8 CAPLUS
CN L-Aspartic acid, 3-[[3-[(4-cyanobenzoyl)amino]phenyl]methoxy]-, (35)
CCA 1NDEX NAME)

Absolute stereochemistry.

RN 480439-73-4 CAPLUS

Instant is a 371 of PCT/JP2005/05600 (03/18/2005)

10593034

=> s 14 L6 13 L4

 \Rightarrow d ibib abs hitstr 1-13

L6 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2010:168084 CAPLUS ACCESSION NUMBER: 2010:168084 CAPLUS
DOCUMENT NUMBER: 152:279363
TITLE: Inhibitory effects of (2s, 3s)-3-(3-(4 (trifluoromethyl)benzylamino]benzyloxylaspartate (TFB-TBCA) on the astrocytic sodium responses to glutamate

AUTHOR(S): Bozzo, Luigi; Chatton, Jean-Ywes
CORPORATE SOURCE: Department of Physiology, University of Lausanne, Switz.

SOURCE: Brain Research (2010), 1316, 27-34
CODEN: BRFRAP; ISSN: 0006-8993
PUBLISHER: Document of Department of Physiology University of Lausanne, Switz.

Brain Research (2010), 1316, 27-34
CODEN: BRFRAP; ISSN: 0006-8993
Elsewier B.V.
DOCUMENT TYPE: Dournal
ABB Astrocytes are responsible for the majority of the clearance of extracellular glutamate released during neuronal activity, DL-Threo-β-benzyloxyaspartate (TBCA) is extensively used as inhibitor of glutamate transport activity, but suffers from relatively low affinity for the transporter. Here, we characterized the effects of (2s, 38)-3-[3-[4-(trifluoromethyl)benzoylamino]benzyloxy]aspartate (TFB-TBCA), a recently developed inhibitor of the glutamate transporter on mouse cortical astrocytes in primary culture. The glial Na+-glutamate transport DOCUMENT NUMBER: 152:279363 transport system is very efficient and its activation by glutamate causes rapid intracellular Na+ concentration (Na+ i) changes that enable real time of transporter activity. Na+i was monitored by fluorescence microscopy in single astrocytes using the fluorescent Na+-sensitive probe sodium-binding benzofuran isophtalate. When applied alone, TFB-TBOA, at a concentration of 1 entration of 1 µM, caused small alterations of Na+i. TFB-TBCA inhibited the Na+i response evoked by 200 µM glutamate in a concentration-dependent manner with IC50 value of 43 \pm 9 nM, as measured on the amplitude of the Na+i response. The maximum inhibition of glutamate-evoked Na+i increa. TFB-TBOA was > 80%, but was only partly reversible. The residual response onse
persisted in the presence of the AMPA/kainate receptor antagonist CNQX.
TFB-TBOA also efficiently inhibited Na+1 elevations caused by the
application of D-aspartate, a transporter substrate that does not ate non-NMDA ionotropic receptors. TFB-TBOA was found not to influence the membrane properties of cultured cortical neurons recorded in whole-cell patch clamp. Thus, TBB-TBOA, with its high potency and its apparent lack of neuronal effects, appears to be one of the most useful pharmacol. tools s available so far for studying glial glutamate transporters.
480439-73-4, TFB-TBOA
RL: PAC (Pharmacological activity), BIOL (Biological study)
(inhibitory effects of (2S, 3S)-3-[3-[4(trifluoromethyl)benzoylamino]benzyloxy]aspartate (TFB-TBOA) on

Japan La actu, 3-[[3-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, (3S)- (CA INDEX NAME) Absolute stereochemistry OS.CITING REF COUNT: THERE ARE 1 CAPLUS RECORDS THAT CITE THIS (1 CITINGS)
THERE ARE 16 CITED REFERENCES AVAILABLE FOR REFERENCE COUNT: RECORD, ALL CITATIONS AVAILABLE IN THE RE FORMAT

(Continued)

ANSWER 1 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN astrocytic sodium responses to glutamate) 480439-73-4 CAPLUS L-Aspartic acid,

L6 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2008:526914 CAPLUS OSC OMPRIGHT 2011 ACS on STN 2008:526914 CAPLUS 149:97846 Fragmental modeling of human glutamate transporter EAAT1 and analysis of its binding modes by docking OCUMENT NUMBER: pharmacophore mapping
Pedraetti, Alessandro; De Luca, Laura; Sciarrillo,
Cristina; Vistoli, Giulio
Istituto di Chimica Farmaceutica e Tossicologica
"Pietro Pratesi", Facolta di Farmacia, Universita
degli Studi di Milano, Milan, I-20133, Italy
ChemNedChem 200333 3(1), 79-90
CODEN: CHEMOK; ISSN: 1860-7179
Wiley-VCH Verlag CmbH AUTHOR(S): CORPORATE SOURCE: PUBLISHER: Journal English The objective of the study was to generate a reliable model of the homotrimeric structure for the human glutamate transporter EAATI, based AB

exptl. folding of transporter homolog from Pyrococcus horikoshii. The monomer structure was derived using a fragmental approach and the homotrimer was assembled using protein-protein docking. The interaction capacities of the EARTI model were explored by docking a set of 32 known ligands including both substrates and blockers. Docking results unveiled that the substrates' bloactivity is strongly influenced by a precise fitting between the ligand and the EARTI binding site, whereas the blockers' activity depends on a set of apolar contacts that ligands can realize in an adjacent hydrophobic subpocket. The docking results were further verified by generating two pharmacophore models (the first for substrates and the latter for blockers) which revealed the features necessary for high EARTI activity. The consistency of docking results

the agreement with pharmacophore models afford an encouraging validation for the EAATI model and emphasize the soundness of the fragmental approach

pach to model any transmembrane protein 480439-66-5 480439-69-8 480 IT 480439-73-4.

480.439-66-5 480.439-69-8 480.439-73-4,
TFB-TBOA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(fragmental modeling of human glutamate transporter EAAT1 and anal. of
its binding modes by docking and pharmacophore mapping)
480.439-66-5 CAPLUS
L-Aspartic acid, 3-[[3-[(4-methoxybenzoyl)amino]phenyl]methoxy]-, (3S)(CA INDEX NAME)

Absolute stereochemistry

ANSWER 2 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued) 480439-69-8 CAPLUS L-Aspartic acid, 3-[[3-[(4-cyanobenzoy1)amino]phenyl]methoxy]-, (3S)-

Absolute stereochemistry.

INDEX NAME)

480439-73-4 CAPLUS TO 40439-73-4 CAPLOS

CN L-Aspartic acid,
3-[[3-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy], (3S)- (CA INDEX NAME)

Absolute stereochemistry.

OS.CITING REF COUNT: RECORD THERE ARE 4 CAPLUS RECORDS THAT CITE THIS

(4 CITINGS)
THERE ARE 51 CITED REFERENCES AVAILABLE FOR REFERENCE COUNT:

DOCUMENT NUMBER: TITLE:

CORPORATE SOURCE:

10593034

L6 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

DOCUMENT NOMER: 146:244722

TITLE: Characterization of the tritium-labeled analog of L-threo-β-benzyloxyaspartate binding to glutamate transporters

AUTHOR(S): Shimamoto, Keiko; Otsubo, Yasuto; Shigeri, Yasushi; Yasuda-Kamatani, Yoshimi; Satoh, Mazamichi; Kaneko, Shiji, Nakagawa, Takayuki

CORPORATE SOURCE: Suntory Institute for Bioorganic Research, Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka, Japan Molecular Pharmacology (2007), 71(1), 294-302 (200EN: MOMER) (200EN: MOMER) (200F), 71(1), 294-302 (200EN: MOMER) (200F), 71(1), 294-302 (200EN: MOMER) (200EN: MOMER) (200F), 71(1), 294-302 (200EN: MOMER) (200EN: MOMER) (200F), 71(1), 294-302 (200EN: MOMER) (single class of noncooperative binding sites for Na+, suggesting that Na+ binding in the ligand binding step is different from Na+ binding in the substrate in the ligand binding are displaced by known substrates and in the ligand binding step is different from Na+ binding in the substratuptake process. The binding was displaced by known substrates and blockers. The rank order of inhibition by these compds. was consistent with glutamate uptake assay results reported previously. Thus, the [3H]ETB-TBOA binding assay will be useful to screen movel EAAT ligands all EAAT subtypes. all EAAT subtypes.
864937-05-3P
RL: ARG (Analytical reagent use); PRT (Pharmacokinetics); SPN (Synthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses) (characterization of tritium-labeled analog of L-threo-β-benzyloxyaspartate binding to glutamate transporters)
864937-05-3 CAPLUS
L-Aspartic acid, 3-[[3-[[4-(ethyl-1,2-t2)benzoyl]amino]phenyl]methoxy]-, (3S)- (CA INDEX NAME)

L6 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2007:22602 CAPLUS

2007:22602 CAPLUS 146:244722

Characterization of the tritium-labeled analog of

Absolute stereochemistry

ANSWER 3 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

.CITING REF COUNT: THERE ARE 6 CAPLUS RECORDS THAT CITE THIS (6 CITINGS)
THERE ARE 39 CITED REFERENCES AVAILABLE FOR REFERENCE COUNT: RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 4 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2006:658062 CAPLUS
145:124841
Preparation of β-benzyloxyaspartic acid
derivatives as affinity-column ligands and glutamic
Michael Capan
Shimamoto, Keiko
Suntory Linited Japan
CODEN: PIXXD2
PATENT
Japanese
1 DOCUMENT NUMBER: NVENTOR(S): ATENT ASSIGNEE(S): LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

PATENT NO KIND DATE APPLICATION NO. WO 2006070737 20060713 JP 2004-377557 20041227 JP 2006182696 A 20060713 B2 20071114 JP 4008446 EP 2005-820230 20051226 EP 1849766 A1 20071031 EP 1849/66 A1 2007/051 EP 2003-820230 2005/1226 R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IZ, IS, IT, II, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR US 20080070321 A1 20080320 US 2007-94124 20070626 B2 20100302 US 7670784 PRIORITY APPLN. INFO.: JP 2004-377557 A 20041227 WO 2005-JP23773 W 20051226

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT OTHER SOURCE(S): MARPAT 145:124841 OTHER SOURCE(S):

PAGE 1-A

PAGE 1-B

(Continued)

10593034

```
ANSWER 4 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued) diazaoctacos-1-yl)amino]-5-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, (3S)-, bis(trifluoroacetate) (9CI) (CA INDEX NAME)
 L6 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN
                                                                                                                                                  (Continued)
                                                                                                                                                                                                                                                  CM 1
                                                                                                                                                                                                                                                  CRN 896712-89-3
CMF C41 H59 F3 N6 O13
                                                                                                                                                                                                                                     Absolute stereochemistry. Rotation (-).
                                                                                                                                                                                                                                                       HO2
AB Title compds. I [R1 = (un)substituted aromatic group, R2 = (un)substituted
             linear or branched aliphatic group optionally having nitrogen or oxygen
 in
             the chain, (un)substituted aromatic group] and salts thereof were
the chain, (un)substituted aromatic group] and saits thereo
prepared For example, treatment of compound II [R = tert-butyl, R' =
tert-butoxycarbonyl] with trifluoroacetic acid afforded compound II [R, R' = H]
trifluoroacetic
with trifluoroacetic acid afforded compound II [R, R' = H] trifluoroacetic acid salt in 94% yield. In glutamic acid uptake inhibition assays, ICSO values of compound II [R, R' = H] \cdotCT3CO2H for ZAAT2 and EAAT3 were 1.3 and 0.46 mM, resp. A method of purifying or detecting an L-glutamic acid transporter using compds. I is provided. IT 896712-90-6P 896712-92-8P 896712-94-0P RLi ARG (Analytical reagent use), BUU (Biological use, unclassified), PAC (Pharmacological activity), SPN (Synthetic preparation); THU (Therapeutic use), NNST (Analytical study); BIOL (Biological study); PREF (Preparation); USES (Uses) (preparation of \beta-benzyloxyaspartic acid derivs. as affinity-column ligands and glutamic acid transporter inhibitors) RN 836712-90-6 CAFLUS CN L-Aspartic acid, 3-[[3-[(28-amino-1,8,15-trioxo-17,20,23,26-tetraoxa-7,14-
                                                                                                                                                                                                                                                  CM 2
                                                                                                                                                                                                                                                  CRN 76-05-1
CMF C2 H F3 O2
            ANSWER 4 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN
                                                                                                                                                      (Continued)
                                                                                                                                                                                                                                                 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN CRN 896712-93-9
                                                                                                                                                                                                                                                  CRN 896712-93-9
CMF C22 H22 F3 N3 O7
                                                                                                                                                                                                                                      Absolute stereochemistry
             896712-92-8 CAPLUS
L-Aspartic acid, 3-[3,5-bis[4-
(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, (3S)-,
mono(trifluoroacetate) (9CI) (CA INDEX NAME)
             CRN 896712-91-7
CMF C27 H21 F6 N3 O7
 Absolute stereochemistry.
 F3C
                                                                                                                                                                                                                                                  CM
                                                                                                                                                                                                                                                             2
                                                                                                                                                                                                                                      F-C-CO2H
                                                                                                                                                                                                                                    IT
                                                                                                                                                                                                                                                  896713-01-2
                                                                                                                                                                                                                                                 896713-01-2 RL: RCT (Reactant); RACT (Reactant or reagent) (preparation of \beta-benzyloxyazpartic acid derivs. as affinity-column liqands and glutamic acid transporter inhibitors) 896713-01-2 CAPLUS L-Aspartic acid, 3-[[3,5-bis[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-N-[(1,1-dimethoxycarbonyl]-, bis(1,1-dimethylethoxy) ester, (3S)- (9CI) (CAINDEX NAME)
             CM 2
             CRN 76-05-1
CMF C2 H F3 O2
                                                                                                                                                                                                                                     Absolute stereochemistry.
             896712-94-0 CAPLUS L-Aspartic acid, 3-[[3-[(1-oxopropy1)amino]-5-[[4-(trifluoromethy1)benzoy1]amino]phenyl]methoxy]-, (3S)-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)
```

ANSWER 4 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

896713-00-1P 896713-02-3P 896713-03-4P RL: RCT (Reactant); SPN (Synthetic preparation); FREP (Preparation); RACT (Reactant or reagent) (preparation of β-benzyloxyaspartic acid derivs. as affinity-column ligands and glutamic acid transporter inhibitors) 836713-00-1 CAPLUS L-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-3-[[3-[(32,32-dimethyl-1,8,15,30-tetraoxo-17,20,23,26,31-pentaoxa-7,14,29-trlazatritriacont-1-yl)aminoj-5-[[4-(trifluoromethyl)benzoyl]aminoj|penyl]methoxyl-, bis(1,1-dimethylethyl) ester, (38)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

ANSWER 4 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

OS.CITING REF COUNT: THERE ARE 1 CAPLUS RECORDS THAT CITE THIS

(4 CITINGS)
THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE REFERENCE COUNT:

FORMAT

ANSWER 4 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

$$\begin{array}{c|c} \text{(CH2)} & \text{S} & \text{NH} \\ \text{O} & \text{CH2} & \text{S} & \text{OBu-t} \\ \text{O} & \text{CF3} & \text{CF3} \end{array}$$

896713-02-3 CAPLUS L-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-3-[[3-[(1-oxo-2-propenyl)amino]-5-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, bis(1,1-dimethylethyl) ester, (3S)- (9CI) (CA INDEX NAME)

896713-03-4 CAPLUS

Sec 13-33-4 ARIUS ARIUS (1,1-dimethylethoxy)carbonyl]-3-[[3-[(1-oxopropyl)amino]-5-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, bis(1,1-dimethylethyl) ester, (3)- (921) (CA INDEX NAME)

Absolute stereochemistry.

L6 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2006:129293 CAPLUS

DOCUMENT NUMBER:

AUTHOR(S):

CORPORATE SOURCE:

SOURCE:

ANSWER 5 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN
DESIGN NUMBER: 2006:129293 CAPLUS
MENT NUMBER: 144:324958

E: Elucidation of glutamate transporter functions using selective inhibitors
SOR(S): Shimamoto, Keiko
SORATE SOURCE: Suntory Institute for Bioorganic Research, 1-1-1
Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka, 618-8503, Japan Shinkei Kenkyu no Shinpo (2005), 49(6), 850-854
CODEN: SKNSAF; ISSN: 0001-8724
ISHER: Jaku Shoin Ltd.
MENT TYPE: Journal; General Review
BUNGE: A review. L-Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system(CNS). To terminate glutamate receptor activation and to protect neurons from excitotoxicity, extracellular glutamate conces. are strictly controlled by sodium dependent glutamate transporters (excitatory amino acid transporters 1-5: EAATS1-5) located in nerve endings and surrounding glia cells. Selective and potent inhibitors have served as important exptl. tools to identify the physiol. roles of transporters in the regulation of synaptic transmission or in

pathogenesis of neurol diseases. A pharmacol useful probe, threo- β -benzyloxyaspartate (DL-TBOA) which functions as a non-transportable blocker for all subtypes of EAATs, has emerged from modification of a known inhibitor threo- β -hydroxyaspartate (THA). Non-transportable blockers are indispensable because, unlike substrates, they do not cause heteroexchange. By comparing the effects of substrates and non-transportable blockers, physiol. roles of EAATs have been revealed. EAATs not only remove transmitter from synaptic clefts but

also actively modulate neurotransmission. Moreover, higher affinity ligands have been developed as novel pharmacol. tools. TBOA analogs possessing a bulky substituent on their benzene ring significantly inhibited labeled glutamate uptake, the most potent of compound being (23, 33)-3-(3-(4-(tri-fluoromethyl) benzoyl-amino) benzyloxy) aspartate (TFB-TBOA). TFB-TBOA is genuinely non-transportable at ED and showed no effects on glutamate receptors. TFB-TBOA would be a suitable lead ound

mpound
for designing functionalized ligands from the perspective of its markedly
high affinity for EAAT proteins.

480439-73-4, TEB-TBCA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(elucidation of glutamate transporter functions using selective
inhibitors)

480439-73-4 CAPLUS
L-Aspartic acid,
[[3-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy], (3S)- (CA INDEX NAME)

Absolute stereochemistry

ANSWER 5 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

ANSWER 6 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

.CITING REF COUNT:

REFERENCE COUNT:

FORMAT

THERE ARE 7 CAPLUS RECORDS THAT CITE THIS

(7 CITINGS)
THERE ARE 37 CITED REFERENCES AVAILABLE FOR

RECORD. ALL CITATIONS AVAILABLE IN THE RE

L6 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2006:58482 CAPLUS

2006:58482 CAPLUS 144:429643

DOCUMENT NUMBER:

CORPORATE SOURCE:

TITLE: Roles of glial glutamate transporters in shaping

at the climbing fiber-Purkinje cell synapses Takatsuru, Yusuke; Takayasu, Yukihiro; Iino, Masae; Nikkuni, Osamu; Ueda, Yuto; Tanaka, Kohichi; Ozawa, AUTHOR(S):

Nikkuni, Osamu, Osamu, Seiji
Department of Neurophysiology, Gunma University
Graduate School of Medicine, Maebashi, Gunma,
371-8511, Japan
Neuroscience Research (Amsterdam, Netherlands)

Neuroscience Research (Amsterdam, Netherlands)

(2006),

54(2), 140-148

CODEN: NERADN; ISSN: 0168-0102

PUBLISHER: Elsewier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Glial glutamate transporters, GLAST and GLT-1, are co-localized in processes of Bergmann glia (BG) wrappling excitatory synapses on Purkinge cells (PCs). Although GLAST is expressed six-fold more abundantly than GLT-1, no change is detected in the kinetics of climbing fiber (CF)-mediated excitatory postsynaptic currents (CF-EPCS) in PCs in GLAST(-/-) nice compared to the wild-type mice (WT). Here we aimed to clarify the mechanism(s) underlying this unexpected finding using a selective GLT-1 blocker, dihydrokainate (DHK), and a novel antagonist of glial glutamate transporter, (2S,3S)-3-(3-(4-methoxybenzoylamino)benzyloxy]aspartate (PMB-TBOA). In the presence of cyclothiazide (CTZ), which attenuates the desensitization of AMPA receptors, DBK prolonged the decay time constant (tw) of CF-EPSCs in WT, indicating that GLT-1 plays a partial role in the removal of glutamate. The application of 100 nm PMM-TBOA, which inhibited CF-mediated transporter currents in BG by .apprx.30%, caused no change in t w in WT in the absence of CTZ, whereas it prolonged t w in the presence of CTZ. This prolonged value of tw was similar to that in GLAST(-/-) mice in the presence of CTZ. There results indicate that glial glutamate transporters can apparently retain the fast decay kinetics of CF-EPSCs if a small proportion (.apprx.20%) of functional transporters is preserved.

IT 480439-66-5

ELB SU (Biological study, unclassified); BIOL (Biological study) (glial glutamate transporter arranguater.

480439-66-5
EL; BSU (Biological study, unclassified); BIOL (Biological study)
(glial glutamate transporter antagonist
(23,35)-3-[3-(4-methoxybenzoylamino) benzyloxy]aspartate inhibited
CF-mediated transporter currents in Bergmann glia and prolonged decay
time constant in presence of cyclothiaride in GLAST(-/-) mouse)
480439-66-5 CAPLUS
L-Aspartic acid, 3-[[3-[(4-methoxybenzoyl)amino]phenyl]methoxy]-, (38)(CA INDEX NAME)

Absolute stereochemistry

L6 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2006:24201 CAPLUS

L6 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER:

DOCUMENT NUMBER:

TITLE:

144:14287

Facilitative effect of a glutamate transporter inhibitor (2s,3s)-3-(3-(4-(trifluoromethyl)benzoylamino]benzyloxy}aspartate on the expression of methamphetamine-induced behavioral sensitization in rats

AUTHOR(S):

FUJio, Masumini, Nakagawa, Takayuki, Suzuki, Yuichi, Satoh, Masamindi, Kaneko, Shuji

Department of Molecular Pharmacology, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, 606-8501, Japan

Journal of Pharmacological Sciences (Tokyo, Japan) (2005), 99(4), 415-418

COEM: JESTGJ, ISSN: 1347-9613

JOURNAL TYPE:

LANGUAGE:

Briglish

B We examined the effects of a potent glutamate transporter inhibitor, (2s,3s)-3-(3-(4-(trifluoromethyl)benzoylamino]benzyloxy|aspartate (TTB-TBOA), on the expression of methamphetamine-induced behavioral sensitization in rats. Rats were i.p. treated with 2 mg/kg methamphetamine for 5 days and then challenged with 1 mg/kg methamphetamine. Intracerebroventricular administration of TTB-TBOA (0.1 nmol) 10 min before the challenge significantly facilitated the expression of behavioral sensitization. It had no effect on the locomotor expression

of behavioral sensitization. It had no effect on the locomotor activation

vation elicited by the challenge with methamphetamine in repeated-saline-treated (non-sensitized) rats. These results suggest that central glutamate transporters may play an inhibitory role in the expression of behavioral sensitization to methamphetamine.

IT 480439-73-4

RL: PAC (Pharmacological activity); BIOL (Biological study)

(facilitative effect of a glutamate transporter inhibitor

{[(trifluoromethyl)benzoylamino]benzyloxy|aspartate on expression of methamphetamine-induced behavioral sensitization in rats)

RN 480439-73-4 CAPLUS

CN L-Aspartic acid,
3-[(3-[(4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]
, (3S)- (CA INDEX NAME)

Absolute stereochemistry

OS.CITING REF COUNT: RECORD 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS

L6 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued) (1 CITINGS)

THERE ARE 15 CITED REFERENCES AVAILABLE FOR REFERENCE COUNT: RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

INSTANT APPLICATION

ANSWER 8 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2005:1042190 CAPLUS DOCUMENT NUMBER: 143:306541 Preparation of radiolabeled TITLE: 3-[3-(benzoylamino)benzyloxy]aspartic acid derivatives as glutamate transporter inhibitors
Shimamoto, Keiko; Saji, Hideo; Kuge, Yuji; Ueda,
Masashi; Satoh, Masamichi; Nakagawa, Takayuki
Suntory Limited, Japan
PCT Int. Appl., 47 pp.
CODEN: PIXXD2
Patent
English 1
1 INVENTOR (S): PATENT ASSIGNEE(S): DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM, COUNT: PATENT INFORMATION: PATENT NO. KIND DATE APPLICATION NO. W0 2005090268 Al 20050929 W0 2005-JP5600 20050318
W: AR, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EZ, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, II, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MX, MN, MW, MX, MZ, NA, NI, NO, NZ, CM, FG, PH, FL, FT, FO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TN, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FF, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

1732864 Al 20061220 EP 2005-721527 20050318

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LI, LU, MC, NL, PL, FT, RO, SE, SI, SK, TR

2007529412 T 2007529318 EP 1732864 2007529412 20071025 US 20080248485 PRIORITY APPLN. INFO.: A1 20081009 WO 2005-JP5600

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT CHER SOURCE(S): CASREACT 143:306541; MARPAT 143:306543 AB The invention provides a radiolabeled liqand which is highly selective

potent for glutamate transporters and is usable in specifically detecting the glutamate transporter. Specifically, the invention provides 3-[3-(benzoylamino)benzyloxy]aspartic acid (BzA-TBOA) having a radioactive

radioactive substituent at the p-position of the benzoyl group, as well as esters or salts. Thus, [1251]I-BzA-TBOA was prepared from N,O-protected A-TBOA by acylation with 4-bromobenzoyl chloride, tributylstannylation, substitution

reaction with Na1251, and deprotection. Glutamate transporter inhibitory activity data are tabulated for compds. of the invention.

ANSWER 8 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued) 864936-98-1P 864936-99-2P 864937-01-99 864937-04-2P RL: DGN (Diagnostic use); SFN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of radiolabeled [(benzoylamino)benzyloxy]aspartic acid vs.

as glutamate transporter inhibitors)
864936-98-1 CAPIUS
L-Aspartic acid, 3-[[3-[[4-(iodo-l251)benzoyl]amino]phenyl]methoxy]-,
(38)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

864936-99-2 CAPLUS L-Aspartic acid, 3-[[3-[(4-iodobenzoyl)amino]phenyl]methoxy]-, (3S)- (CAINDEX NAME)

Absolute stereochemistry.

864937-01-9 CAPLUS Sody3/-UL-9 CAPLOS L-Aspartic acid, 3-[[3-(benzoyl-4-t-amino)phenyl]methoxy]-, (3S)- (9C1) (CA INDEX NAME)

Absolute stereochemistry

ANSWER 8 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

864937-04-2 CAPLUS L-Aspartic acid, 3-[[3-[(4-ethylbenzoyl)amino]phenyl]methoxy]-, (3S)-INDEX NAME)

Absolute stereochemistry.

480439-71-2 IT 480439-73-4 864937-05-3D. tritium-labeled
RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); (preparation of radiolabeled [(benzoylamino)benzyloxy]aspartic acid derivs.

as glutamate transporter inhibitors)
480439-71-2 CAPLUS
L-Aspartic acid, 3-[[3-[(4-fluorobenzoyl)amino]phenyl]methoxy]-, (3S)(CA INDEX NAME)

Absolute stereochemistry

ANSWER 8 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

RN 480439-73-4 CAPLUS
CN L-Aspartic acid,
3-[[3-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy], (3S)- (CA INDEX NAME)

Absolute stereochemistry.

864937-05-3 CAPLUS L-Appartic acid, 3-[[3-[[4-(ethy1-1,2-t2)benzoy1]amino]pheny1]methoxy]-, (33)- (CA INDEX NAME)

Absolute stereochemistry.

L6 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN Absolute stereochemistry. (Continued)

 $864937-02-0 \quad {\tt CAPLUS} \\ \texttt{L-Aspartic acid}, \ \texttt{N-[(1,1-dimethylethoxy)carbonyl]-3-[[3-[(4-ethenylbenzoyl)amino]phenyl]methoxy]-, } bis(1,1-dimethylethyl) ester,$ RN CN (3S) -

(9CI) (CA INDEX NAME) Absolute stereochemistry.

864937-03-1 CAPLUS L-Aspartic acid, 3-[[3-[(4-ethenylbenzoyl)amino]phenyl]methoxy]-, (3S)-(CA INDEX NAME)

Absolute stereochemistry

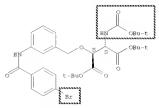
EXR: Michael Barker

ANSWER 8 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

864936-96-9P 864936-97-0P 864937-02-0P 864937-03-1P 864937-00-8P REL: RCT (Reactant); SPN (Synthetic preparation); FREP (Preparation); RACT (Reactant or reagent) (preparation of radiolabeled [(benzoylamino)benzyloxy]aspartic acid

vs.
as glutamate transporter inhibitors)
864936-96-9 CAPLUS
L-Aspartic acid, 3-[[3-[(4-bromobenzoyl)amino]phenyl]methoxy]-N-[(1,1-dimethylethoxy)carbonyl]-, bis(1,1-dimethylethyl) ester, (38)- (9CI) (CA INDEX NAME)

Absolute stereochemistry



864936-97-0 CAPLUS
L-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-3-[[3-[[4-(tributylstannyl)benzoyl]amino]phenyl]methoxy]-, bis(1,1-dimethylethyl)ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

864937-00-8 CAPLUS L-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-3-[[3-[(4-iodobenzoyl)amino]phenyl]methoxy]-, bis(1,1-dimethylethyl) ester, (3S)-(9CI) (CA INDEX NAME)

L6 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L6 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN ACCESSION NUMBER: 2005:299120 CAPLUS 142:442183
A novel L-glutamate transporter inhibitor reveals endogenous D-aspartate homeostasis in rat pheochromocytoma MPT1 cells
Koyama, Hayato; Sekine, Masae; Furuchi, Takemitsu; Katane, Masumi; Nimura, Noriyuki; Shimamoto, Keiko; Nakajima, Terumi; Homma, Hiroshi School of Pharmaceutical Sciences, Kitasato University, Minato-ku, Tokyo, 108-8641, Japan Life Sciences (2005), 76(25), 2933-2944
CODEN: LIFSAK; ISSN: 0024-3205
Elsevier B.V.
Journal DOCUMENT NUMBER: TITLE: AUTHOR(S): CORPORATE SOURCE: SOURCE ODEN: LIFSAR; ISSN: 0024-3203

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We previously reported for the first time that D-aspartate (D-Asp) is biosynthesized by cultured mammalian cells such as pheochromocytoma cells and its subclone MFTI (FEBS Lett. 434 (1998) 231, Arch. Biochem. Biophys. 404 (2002) 92). We speculated that D-Asp levels in the intra-and extracellular spaces of the cultured cells are maintained in a Blophys. 404 (2012) %21. We apcounted and extracellular spaces of the cultured cells are maintained in a dynamic state of homeostasis. To test this here, we utilized a novel and potent L-Glu transporter inhibitor, (28,78)-3-{3-[4-(trifluoromethyl)benzyloxylamino]benzyloxy]aspartate (TFB-TBOR). This inhibitor proved to be a genuine nontransportable blocker of the transporter even during long periods of culture. Use of this inhibitor with MFTI cells confirmed that D-Asp levels are in a dynamic steady state where it is constantly released into the extracellular space by a yet undefined mechanism as well as being constantly and intensively taken up by the cells via the L-Glu transporter. We estimated the rate with which D-Asp is constitutively released from MFTI cells is approx. 3.8 pmol/h/1 x 105 cells.

If 480439-73-4
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); BIOL (Biological study); USES (Uses) (glutamate transporter inhibitor reveals endogenous D-aspartate homeostasis in rat pheochromocytoma MFTI cells)

RN 480439-73-4 CAPLUS
CN L-Aspartic acid, 3-[[3-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, (38)- (CA INDEX NAME)

Absolute stereochemistry.

OS.CITING REF COUNT: THERE ARE 7 CAPLUS RECORDS THAT CITE THIS (7 CITINGS)
THERE ARE 42 CITED REFERENCES AVAILABLE FOR REFERENCE COUNT: RECORD. ALL CITATIONS AVAILABLE IN THE RE

(Continued)

(Continued)

ANSWER 9 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN

PLUS COPYRIGHT 2011 ACS on STN 2005;214287 CAPLUS 143:146338 Effects of a novel glutamate transporter blocker, (2S,3S)-3-43-[4- (trifiluoromethyl)benzoylamino]benzyloxylaspartate (TFB-TBAA), on activities of hippocampal neurons Tsukada, Shota; Iino, Masse; Takayasu, Yukihiro; Shimamoto, Keiko; Cawak, Seiji Department of Neurophysiology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebaahi, Gunma, 371-8511, Japan Neuropharmacology (2005), 48(4), 479-491 CODEN NEPHBW, ISSN: 0028-3908 Elsevier B.V. Journal JMENT NUMBER: AUTHOR(S): CORPORATE SOURCE: PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Glutamate transporters rapidly take up synaptically released glutamate maintain the glutamate concentration in the synaptic cleft at a low level. (28, 38)-3-(3-(4-(trifluoromethyl)benzoylamino]benzyloxylaspartate (TFB-TBOA) is a novel glutamate transporter blocker that potently suppresses the activity of glial transporters. TFB-TBOA inhibited synaptically $\frac{1}{2}$ activated transporter currents (STCs) in astrocytes in the stratum radiatum in rat hippocampal slices in a dose-dependent manner with an IC50 of 13 nM, as reduced them to approx. 10% of the control at 100 nM. We investigated effects of TFB-TBOA on glutamatergic synaptic transmission and cell excitability in CAI pyramidal cells. TFB-TBOA (100 nM) prolonged the decay of N-methyl--aspartic acid receptor (NMDAR)-mediated excitatory postsynaptic currents (EPSCs), whereas it prolonged that of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-mediated EPSCs only when the desensitization of AMPARs was need reduc y cyclothiazide (CT2). Furthermore, long-term application of TFB-TBCA nduced spontaneous epileptiform discharges with a continuous epolarization shift of membrane potential. These epileptiform

ANSWER 10 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN SSION NUMBER: 2005:214287 CAPLUS

ACCESSION NUMBER:

activities

were mainly attributed to NMDAR activation. Even after pharmacol block
of NMDARs, however, TFB-TBOA induced similar changes by activating AMPARs
in the presence of CTZ. Thus, the continuous uptake of synaptically
released glutamate by glial transporters is indispensable for protecting
hippocampal neurons from glutamate receptor-mediated hyperexcitabilities.

IT 480439-73-4, TFB-TBOA
RL: PAC (Pharmacological activity); BIOL (Biological study)
(effects of a novel glutamate transporter blocker,
(2S, 3S)-3-{3-[4-(trifluoromethyl)benzoylamino]benzyloxylaspartate
(TTB-TBCA), on activities of hippocampal neurons)

RN 480439-73-4 CAPLUS
CN L-Aspartic acid,
3-[(3-[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy], (3S)- (CA INDEX NAME)

OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
THERE ARE 43 CITED REFERENCES AVAILABLE FOR REFERENCE COUNT: RECORD. ALL CITATIONS AVAILABLE IN THE RE

ANSWER 10 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN

FORMAT

L6 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2004:469790 CAPLUS
DOCUMENT NUMBER: 141:184585
Synthesis of carbamate-type caged derivatives of a novel glutamate transporter blocker
Takaoka, Kiyo; Tatsu, Yoshiro; Yumoto, Noboru;
Nakajima, Terumi; Shimamoto, Keiko
Suntory Institute for Bioorganic Research, 1-1-1
Wakayamadai, Osaka, Shimamoto, 618-8503, Japan
Bioorganic &
CODEN: BIOORGES
CODEN: BIOORGES
CODEN: BIOORGES
COUNTER: CODEN: BMECEP; ISSN: 0968-0896
Elsevier Ltd.
JOURNAL
LANGUAGE: Levier Ltd.
JOURNAL
LANGUAGE: Levier Ltd.
ABD L-threo-B-Benzyloxyaspartate (1-TBOA) and
(28,35)-3-(3-[4-(trifluoromethyl)benzoylamino]benzyloxylaspartate
(L-TFB-TBOA) are potent nontransportable blockers for glutamate
transporters. The authors synthesized a carbamate-type counarin
derivative of
L-TBOA (3a) as a caged blocker and compared 3a with the corresponding

(L-TFF-TBOA) are potent nontrainpolitable backets as transporters. The authors synthesized a carbamate-type coumarin derivative of

L-TBOA (3a) as a caged blocker and compared 3a with the corresponding ester-type analogs 1. The carbamate 3a was less sensitive to photolysis than the ester 1 but was more stable in the aqueous solution The [6,7-bis(carboxymethoxy)-coumarin-4-yl]methylcarbonyl (BCMCMC) group exhibited good results both in photoreactivity and stability. Therefore, the authors examined photolysis of N-BCMCMC-TBOA and N-BCMCMC-TFB-TBOA, which immediately released blockers to show glutamate uptake inhibition.

17 737830-26-1P

RL: PAC (Pharmacological activity), PRF (Properties), SFN (Synthetic preparation), THU (Therapeutic use), BIOL (Biological study), PREP (Preparation), Gsynthesis of carbamate-type caged derivs. of novel glutamate transporter blocker)

RN: 737830-26-1 CAFLUS

CN L-Aspartic acid, N-[[16,7-bis(hydroxymethoxy)-2-oxo-2H-1-benzopyran-4-yl]methoxylcarbonyl]-3-[[3-[[4-(trifluoromethyl]benzoyl]amino]phenyl]methoxyl-, bis(1,1-dimethylethyl) ester, (3S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

ANSWER 11 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

PAGE 1-A

PAGE 1-B

CF3

IT 737830-21-6P 737830-22-7P 811412-49-4P RL: PRP (Properties), RCT (Reactant), SPN (Synthetic preparation), PREP (Preparation), RACT (Reactant or reagent) (synthesis of carbamate-type caged derivs. of novel glutamate transporter blocker)
RN 737830-21-6 CAPLUS
CN L-Aspartic acid, 3-[[3-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, bis(1,1-dimethylethyl) ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

ANSWER 11 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

RN 737830-22-7 CAPLUS
CN L-Aspartic acid,
N-[[[6,7-bis[2-(1,1-dimethylethoxy)-2-oxoethoxy]-2-oxo-2H1-benzopyran-4-yl]methoxy]carbonyl]-3-[[3-[[4(trifluoromethyl)benzoyl]amtho]benzoyl], bis[1,1-dimethylethyl)
ester, (3S)- (3CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

L6 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

PAGE 1-B

811412-49-4 CAPLUS

811412-49-4 CAPLUS
L-Aspartic acid, N-[[[6,7-bis(carboxymethoxy)-2-oxo-2H-1-benzopyran-4-yl]methoxy]carbonyl]-3-[[3-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A

L6 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

PAGE 1-B

737830-20-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of carbamate-type caged derivs. of novel glutamate
transporter blocker;
737830-20-5 CAPLUS
L-Aspartic acid, N-[(1,1-dimethylethoxy)carbonyl]-3-[[3-[[4(trifluoromethyl)benzoyl]amino]phenyl]methoxy]-, bis(1,1-dimethylethyl)
ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

OS CITING REF COUNT:

16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS

REFERENCE COUNT: 26

THERE ARE 26 CITED REFERENCES AVAILABLE FOR

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

ANSWER 12 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued) activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (characterization of novel L-threo-B-benzyloxyaspartate derivs., potent blockers of glutamate transporters)
479690-56-7 CAPLUS
L-Aspartic acid, 3-[[3-[(cyclohexylcarbonyl)amino]phenyl]methoxy]-,

(CA INDEX NAME)

Absolute stereochemistry.

479690-57-8 CAPLUS
L-Aspartic acid, 3-[[3-[[4-(1,1-dimethoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.

480439-63-2 CAPLUS L-Aspartic acid, 3-[[3-(benzoylamino)phenyl]methoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry

480439-64-3 CAPLUS L-Aspartic acid, 3-[[3-[(2-methoxybenzoy1)amino]pheny1]methoxy]-, (3S)-

EXR: Michael Barker

ANSWER 12 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN SSION NUMBER: 2004:292674 CAPLUS

ACCESSION NUMBER:

DOCUMENT NUMBER:

141:16890 Characterization of novel TITLE:

CORPORATE SOURCE:

DOCUMENT NUMBER: 141:1639U

L-threo-\$\beta-benzyloxyaspartate derivatives, potent blockers of the glutamate transporters

AUTHOR(S): Shimamoto, Keiko; Sakai, Ryuichi; Takaoka, Kiyo; Yumoto, Noboru; Nakajima, Terumi; Amara, Susan G.; Shiqeri, Yasushi

CORPORATE SOURCE: Suntoy Institute for Bioorganic Research, Osaka, 618-8503, Japan

Molecular Pharmacology (2004), 65(4), 1008-1015 CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal English

AB Nontransportable blockers of the glutamate transporters are important tools for investigating mechanisms of synaptic transmission.

Di-threo-\$\beta-Benzyloxyaspartate (Di-TPOA) is a potent blocker of all subtypes of the excitatory amino acid transporters (EAATs). We characterized novel 1-TBOA analogs possessing a substituent on their resp.

benzene rings. The analogs significantly inhibited labeled glutamate uptake, the most potent of which was [25,33]-3-[3-[4-(trifluoromethyl)benzoylamino]benzyloxy]aspartate (TBB-TBOA). In an uptake assay using cells transiently expressing EAATs, the IC50 values of TFB-TBOA for EAATI, EAAT2, and EAAT3 were 22, 17, a300 mM, resp. TFB-TBOA was significantly more potent at inhibiting EAAT1 and EAAT2 compared with L-TBOA (IC50 values for EAAT1-3 were 33, 6.2, and 15 µM, resp.). Electrophysiol. analyses revealed that TBOA analogs block the transport-associated currents in all five EAAT subtypes and

block leak currents in EAAT5. The rank order of the analogs for potencies

at inhibiting substrate-induced currents was identical to that observed

the uptake assay. However, the kinetics of TFB-TBOA differed from the kinetics of L-TBOA, probably because of the strong binding affinity. Notably, TFB-TBOA did not affect other representative neurotransmitter transporters or receptors, including ionotropic and metabotropic mate. glutamate

glutamate

receptors, indicating that it is highly selective for EAATs. Moreover, intracerebroventricular administration of the TBOA analogs induced severe convulsive behaviors in mice, probably because of the accumulation of glutamate. Taken together, these findings indicate that novel TBOA analogs, especially TTB-TBOA, should serve as useful tools for elucidating the physiol. roles of the glutamate transporters.

17 479690-56-7 479690-57-8 480439-66-5
480439-63-3 480439-65-4 480439-66-5
480439-67-6 480439-68-7 480439-69-8

480 439 - 70 - 1 480 439 - 73 - 4 480439-71-2 480439-72-3

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

ANSWER 12 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (CA INDEX NAME) (Continued)

RN CN

L-Aspartic acid, 3-[[3-[(3-methoxybenzoyl)amino]phenyl]methoxy]-, (38)-(CA INDEX NAME)

Absolute stereochemistry

480439-66-5 CAPLUS

L-Aspartic acid, 3-[[3-[(4-methoxybenzoyl)amino]phenyl]methoxy]-, (38)-(CA INDEX NAME)

Absolute stereochemistry

480439-67-6 CAPLUS L-Aspartic acid, 3-[[3-[(3,4-dimethoxybenzoyl)amino]phenyl]methoxy]-, (35)- (CA INDEX NAME)

Absolute stereochemistry.

ANSWER 12 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

480439-68-7 CAPLUS L-Aspartic acid, 3-[[3-[([1,1'-bipheny1]-4-ylcarbony1)amino]pheny1]methoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.

480439-69-8 CAPLUS L-Aspartic acid, 3-[[3-[(4-cyanobenzoy1)amino]pheny1]methoxy]-, (3S)-CN (CA INDEX NAME)

Absolute stereochemistry.

480439-70-1 CAPLUS L-Aspartic acid, 3-[[3-[(4-nitrobenzoy1)amino]pheny1]methoxy]-, (3S)-

ANSWER 12 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

RN 480439-73-4 CAPLUS CN L-Aspartic acid, 3-[[3-[[4-(trifluoromethy1)benzoy1]amino]pheny1]methoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.

THERE ARE 44 CAPLUS RECORDS THAT CITE THIS OS . CITING REF COUNT: 44 RECORD (44 CITINGS)
THERE ARE 31 CITED REFERENCES AVAILABLE FOR 31 REFERENCE COUNT: RECORD, ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 12 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

Absolute stereochemistry.

480439-71-2 CAPLUS L-Aspartic acid, 3-[[3-[(4-fluorobenzoy1)amino]pheny1]methoxy]-, (3S)-(CA INDEX NAME)

480439-72-3 CAPLUS TOWNSTRIES CAPLUS
CN L-Aspartic acid,
3-[[3-[[4-(trifluoromethoxy)benzoy1]amino]phenyl]methoxy], (3S)- (CA INDEX NAME)

Absolute stereochemistry.

INVENTOR(S): PATENT ASSIGNEE(S):

DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

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						A1	-	2003	WO 2002-JP6286								20020624				
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											US	200	4-4	4812	37		A3	2004	71:	Э	

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT OTHER SOURCE(S): CASREACT 138:72990; MARPAT 138:72990 OTHER SOURCE(S):

AB L-Threo- β -benzyloxyaspartate derivs. I [R = H, (un)substituted acyl, an amino acid- or biotin-derived group] or their salts were prepared for binding to affinity column chromatog. carriers as ligands of glutamate transporter proteins. Thus, I (R = m-H2NCH2CH2CONH) (AA-TBGA) was prepared by a multistep synthesis starting with the reaction of

L6 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)
(2S,3E)-[3-(benzyloxymethyl)oxiranyl]methyl p-nitrobenzoate with benzoyl
isocyanate. The inhibitory effect of AA-TBOA was detd. to be IC50 = 2.1
† 0.1 μM and 7.9 † 0.76 μM, resp., for uptake of (14)glutamate
by human EAAT2 or EAAT3 stably expressed on MDCK cells or transiently
expressed on COS-1 cells.

IT 479690-56-7P, C-HexA-TBOA 479690-57-8P, TBU-BZA-TBOA
479690-58-9P 480439-63-2P, BZA-TBOA
480439-64-3P, 0-MCO-BZA-TBOA 480439-65-4P,
m-McO-BZA-TBOA 480439-66-5P, p-McO-BZA-TBOA
480439-67-6P, DIMCO-BZA-TBOA 480439-67-PP, Ph-BZa-TBOA
480439-67-6P, DIMCO-BZA-TBOA 480439-70-1P, NOZ-BZa-TBOA
480439-73-4P, CF3-BZa-TBOA 480439-77-3P, Ph-BZa-TBOA
480439-73-4P, CF3-BZa-TBOA 480439-77-3P, CHS-BZa-TBOA
480439-73-4P, A-PenO-BZA-TBOA 480439-77-3P,
BiOA-PENO-BZA-TBOA
RL: PAC (Pharmacological activity) SPN (Synthetic preparation); TBU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(USes)
(Uses)
(Uses)
(Uses)
(Uses)
(Uses)
(Use)
(Dreparation of (aminobenzyloxy)aspartate derivs, as glutamate
transporter
inhibitors)
RN 479690-56-7 CAPLUS
CN L-Aspartic acid, 3-[[3-[(cyclohexylcarbonyl)amino]phenyl]methoxy]-,
(CA INDEX NAME)

Absolute stereochemistry.

RN 479690-57-8 CAPLUS
CN L-Aspartic acid, 3-[[3-[[4-(1,1-dimethoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.

L6 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

RN 480439-65-4 CAPLUS
CN L-Aspartic acid, 3-[[3-[(3-methoxybenzoy1)amino]pheny1]methoxy]-, (3S)-(CA INDEX NAME)

Absolute stereochemistry

RN 480439-66-5 CAPLUS CN L-Aspartic acid, 3-[[3-[(4-methoxybenzoyl)amino]phenyl]methoxy]-, (3S)-(CA INDEX NAME)

Absolute stereochemistry.

RN 480439-67-6 CAPLUS
CN L-Aspartic acid, 3-[[3-[(3,4-dimethoxybenzoyl)amino]phenyl]methoxy]-, (38)- (CA INDEX NAME)

Absolute stereochemistry.

EXR: Michael Barker

L6 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

RN 479690-58-9 CAPLUS
CN L-Aspartic acid, 3-[[3-[(4-heptylbenzoyl)amino]phenyl]methoxy]-, (38)(CA INDEX NAME)

Absolute stereochemistry.

RN 480439-63-2 CAPLUS CN L-Aspartic acid, 3-[[3-(benzoylamino)phenyl]methoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.

RN 480439-64-3 CAPLUS CN L-Aspartic acid, 3-[[3-[(2-methoxybenzoyl)amino]phenyl]methoxy]-, (38)-(CA INDEX NAME)

Absolute stereochemistry.

L6 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

RN 480439-68-7 CAPLUS
CN L-Aspartic acid, 3-[[3-[([1,1'-biphenyl]-4-ylcarbonyl)amino]phenyl]methoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.

Absolute stereochemistry.

RN 480439-70-1 CAPLUS
CN L-Aspartic acid, 3-[[3-[(4-nitrobenzoy1)amino]pheny1]methoxy]-, (3S)(CA INDEX NAME)

Absolute stereochemistry.

ANSWER 13 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

480439-71-2 CAPLUS L-Aspartic acid, 3-[[3-[(4-fluorobenzoyl)amino]phenyl]methoxy]-, (3S)-(CA INDEX NAME)

RN 480439-72-3 CAPLUS
CN L-Aspartic acid,
3-[[3-[[4-(trifiloromethoxy)benzoyl]amino]phenyl]methoxy], (3S)- (CA INDEX NAME)

Absolute stereochemistry.

480439-73-4 CAPLUS

ANSWER 13 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)

 $\begin{array}{lll} 480439-77-8 & \text{CAPLUS} \\ \text{L-Aspartic acid, } 3-[[3-[[4-[[5-[[5-[(3aS,4S,6aR)-hexahydro-2-oxo-lH-thieno[3,4-d]inidazol-4-y1]-1-oxopentyl]amino]pentyl]oxy]benzoyl]amino]phenyl]methoxy]-, (3S)- (CAINDEX NAME)$

Absolute stereochemistry.

PAGE 1-B

THERE ARE 4 CAPLUS RECORDS THAT CITE THIS

EXR: Michael Barker

L6 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2011 ACS on STN (Continued)
CN L-Aspartic acid,
3-[[3-[[4-(trifluoromethyl)benzoyl]amino]phenyl]methoxy], (3S)- (CA INDEX NAME)

Absolute stereochemistry.

480439-74-5 CAPLUS L-Aspartic acid, 3-[[3-[[4-(hexyloxy)benzoyl]amino]phenyl]methoxy]-, (CA INDEX NAME)

480439-76-7 CAPLUS
L-Aspartic acid, 3-[[3-[[4-[(5-aminopentyl)oxy]benzoyl]amino]phenyl]methoxy]-, (3S)- (CA INDEX NAME)

Absolute stereochemistry.

L6 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2011 ACS ON STN (Continued)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT